Action-blindsight in healthy subjects after transcranial magnetic stimulation

Mark Schram Christensen*†‡, Lasse Kristiansen*, James B. Rowe§¶, and Jens Bo Nielsen*‖

*Department of Exercise and Sport Sciences, University of Copenhagen, Nørre Allé 51, DK-2200 København N, Denmark; †Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital, Hvidovre, Kettegård Allé 30, DK-2650 Hvidovre, Denmark; §Department of Clinical Neurosciences, University of Cambridge, Addenbrooke's Hospital, Cambridge CB2 2QQ, United Kingdom; ¶Medical Research Council Cognition and Brain Science Unit, University of Cambridge, 15 Chaucer Road, Cambridge CB2 7EF, United Kingdom; and ‖Department of Neuroscience and Pharmacology, University of Copenhagen, Faculty of Health Sciences, Panum Institute, Blegdamsvej 3, DK-2200 København N, Denmark

Edited by Lawrence Weiskrantz, University of Oxford, Oxford, United Kingdom, and approved November 27, 2007 (received for review June 22, 2007)

Clinical cases of blindsight have shown that visually guided movements can be accomplished without conscious visual perception. Here, we show that blindsight can be induced in healthy subjects by using transcranial magnetic stimulation over the visual cortex. Transcranial magnetic stimulation blocked the conscious perception of a visual stimulus, but subjects still corrected an ongoing reaching movement in response to the stimulus. The data show that correction of reaching movements does not require conscious perception of a visual target stimulus, even in healthy people. Our results support previous results suggesting that an efference copy is involved in movement correction, and this mechanism seems to be consistent even for movement correction without perception.

consciousness | perception | reaching | efference copy

To pick up a cup is a skilful process requiring precise coordination between hand and eye. How would you manage if someone moved the cup just as the lights went out? Would you still be able to reach the cup? Most people would assume not. With the phenomenon of blindsight, patients who are blind to conscious visual perception can still perform visual manual reaching tasks, that is to say that they can respond to visual information even without visual perception (1, 2). This observation suggests that it is possible to perform purposeful goal-directed movements even though conscious visual perception is lost. The published cases of blindsight are caused by lesions in the visual cortex. The patients have some functional vision preserved, such as the ability to detect motion, the ability to point accurately toward flashes of light without conscious visual perception, or the ability to guess above chance whether a stimulus is present or absent in the visual blind field. Here, we provide evidence of blindsight in normal subjects induced by transcranial magnetic stimulation (TMS) during fast reaching movements, and we discuss the neural mechanisms that are responsible for this behavior. In particular, we address the issue of whether an efference copy is involved in movement correction.

Several mechanisms of blindsight have been proposed, including subcortical and alternative cortical networks. For example, studies of cats (3, 4), monkeys (5) and humans (6) have provided evidence of the existence of a subcortical network that enables very fast reaching movements to visual targets, faster than possible by transcortical mechanisms. The network included brainstem nuclei and propriospinal neurons located in the cervical spine.

In contrast, experiments by Milner and Goodale (7) suggest that separate processing in the ventral and dorsal cortical streams may be responsible for blindsight behavior. Damage to the ventral stream may preserve the ability to act toward visual stimuli, but conscious perception of the appearance of the visual object is diminished or absent. In this case, a possible neural pathway, which bypasses the primary visual cortex, is via the superior colliculus through the pulvinar to the parietal motor regions (8). Indirect evidence from humans exists, suggesting that efference copy signals are responsible for correction of fast reaching movements (9), and it has been shown that these corrections can precede conscious awareness of movements during such tasks (10).

To further investigate probable neural correlates underlying corrections of movements without conscious perception, we adopted an experimental design similar to the one used by Castiello *et al.* (10). The subjects were required to reach toward one of three buttons indicated by a light. Initially, the central first light was turned on, and the subjects reached for the central button in all 200 trials. In 40% of the trials, a second light was turned on either to the left or the right, and the subjects then tried to correct the movement in response to this light. To induce virtual blindness, a single pulse of TMS was applied in half of the trials over the visual cortex 80–90 ms after the second light was turned on (11).

A critical point in the study of blindsight-like behavior is to what extent patients and, in our case, normal healthy subjects, are truly blind, without any perceptual experience of the visual stimuli. Simple binary choices, where subjects only respond positively or negatively to whether they have perceived a visual stimulus, have proven not to capture the graded nature of visual perception. We therefore adopted a modified version of the perception awareness scale (12, 13) in which subjects rate the clarity of their perceptual experience on an ordinal scale. Similar subjective measures of clarity have been used in patients (14), and it has proven to be a more indicative measure of perceptual clarity than strict dichotic measures (12, 13). Therefore, to quantify the effect of TMS, one of four arrow-like figures was displayed as the second light. Subjects had to indicate which arrow they had seen if they had perceived a second light and indicate on a 1–5 scale how clearly they had perceived the light, where C1 (clarity level 1) indicates that no light was perceived, and C5 indicates a clear perceptual experience with identification of the arrow orientation.

If blindsight-like behavior can be induced in normal subjects by using TMS (15, 16) we hypothesized that the subjects would still be able to perform corrections to the second light even though they were unable to detect it, as reported by a C1 on the subjective clarity scale. We compared this situation to a control situation where subjects received TMS and performed erroneous corrections without the presence of a second light. If such behavior can be accomplished, we suggest that the neural

NEUROSCIENCE

Author contributions: M.S.C. and J.B.N. designed research; M.S.C., L.K., and J.B.N. performed research; M.S.C. and J.B.R. analyzed data; and M.S.C., J.B.R., and J.B.N. wrote the paper.

The authors declare no conflict of interest.

This article is a PNAS Direct Submission.

‡To whom correspondence should be addressed at: Danish Research Centre for Magnetic Resonance, Copenhagen University Hospital, Hvidovre, Kettegård Allé 30, DK-2650 Hvidovre, Denmark. E-mail: markc@drcmr.dk.

This article contains supporting information online at www.pnas.org/cgi/content/full/0705858105/DC1.

© 2008 by The National Academy of Sciences of the USA

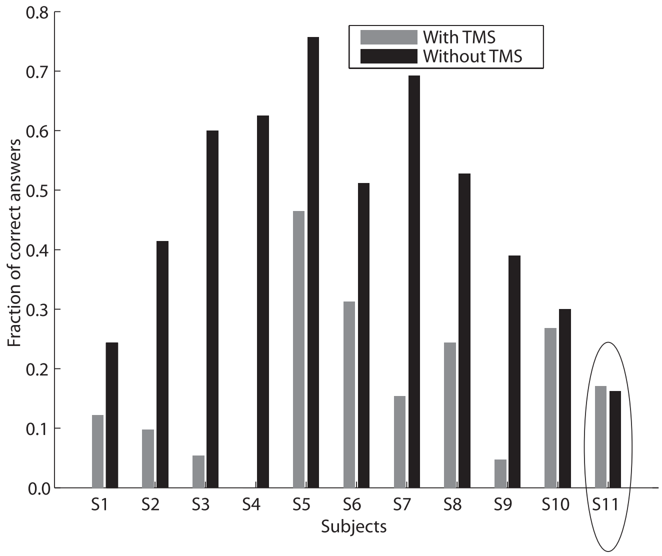

Fig. 1. The fraction of correct answers to the guess of arrow-figure orientation with and without TMS for the individual subjects is shown. All but one subject (circled) made fewer correct responses after TMS.

mechanisms supporting this behavior do not require processing through the visual cortex but may instead bypass visual processing regions and directly influence motor behavior.

It has been suggested that sensory perception and motor control are linked such that perception arises only when interaction with the sensory stimuli are simulated as covert movements (17), a principle that also has been formulated as the theory of event coding (18). Neuroimaging studies have shown that motor regions, such as the intraparietal cortex and premotor cortex are involved in the subjective perceptual experience of visual objects (19, 20). Furthermore, it has been proposed that the lateral intraparietal area is involved in binding of perception and action (21). The present setup investigates both visual perception and motor control and is therefore suited to test whether there is such an interaction between sensory perception and motor control.

We hypothesized that perceptual clarity and motor performance would interact, in particular that the correction reaction time (CRT) or the visuo-motor reaction time (RT) would be influenced by perceptual clarity. Specifically, when perceptual clarity increased motor performance would decrease, reflected in either higher CRT or RT. This relationship is because the networks responsible for perception and action are allocated for either perception or action [see supporting information (SI) *Results*] and, hence, do not perform optimally for both tasks simultaneously. Furthermore, we tested whether the movement time (MT) influences the ability to perform corrective movements and whether corrections gave longer MTs (see SI Fig. 5).

Previous studies have suggested that an efference copy is involved in movement correction, and the measure of that distinction has been that the CRT is lower than the RT (9). We therefore hypothesize that, if an efference copy is involved in movement correction, the CRT will be lower than RT.

Results

TMS Decreases the Ability to Identify the Target Arrow Figures. Of the 11 subjects entering the study, TMS significantly decreased the ability to correctly identify the arrow figure of the second light in 10 subjects (Fig. 1; Wilcoxon rank sum test $P = 0.002$, rank sum = 79). The subject (S11) in whom TMS did not have an effect was omitted from the remaining analyses where the interaction among TMS, clarity, and accuracy was tested. Another subject (S10) perceived phosphenes and was also omitted from further analysis.

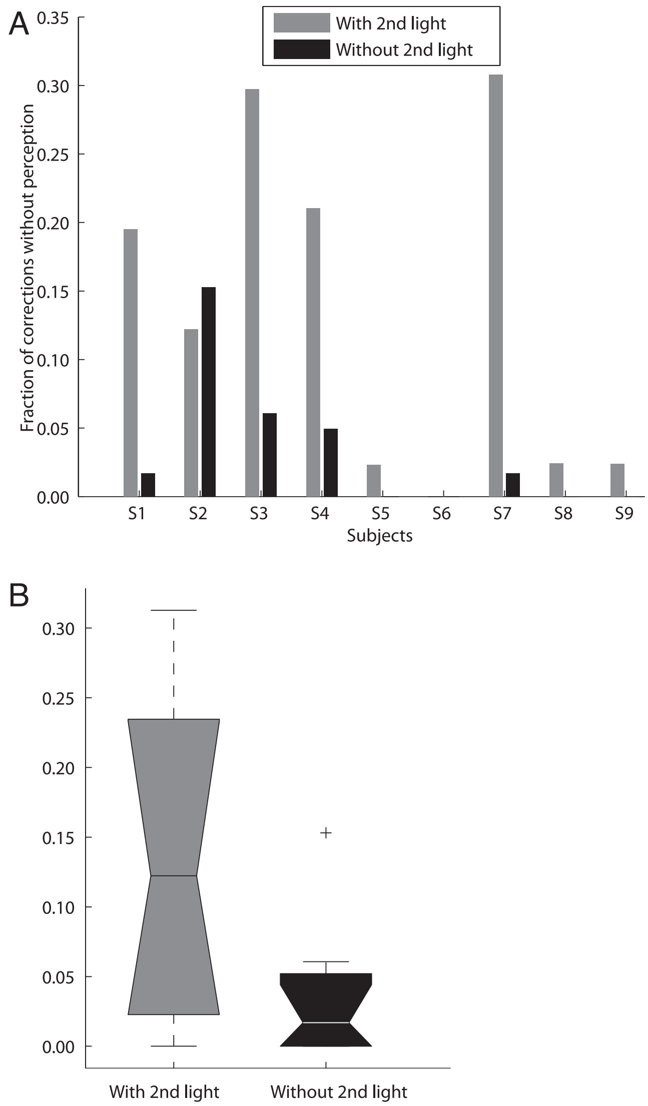

Fig. 2. Corrections without perception. (*A*) The fraction of corrections performed without perception (at clarity level C1) with and without presentation of a second light for each subject. Despite the lack of reported perception, more corrections were made by most subjects when the second light was shown then when it was not shown. (*B*) The fraction of responses made to an unseen side light (at clarity level C1) with and without a second light for the group. The difference between gray and black bars indicates action-blindsight corrections over and above false positive corrections.

Corrections Without Detection. To test whether subjects exhibited blindsight-like behavior, we tested the fraction of correct corrections in the presence of a second light that was not perceived by the subject (i.e., report C1) against the fraction of erroneous corrections without a second light. Only trials in which TMS was applied were included in the analysis. The results are displayed in Fig. 2 *A* and *B*.

The fraction of proper corrections without detection of the presented second light was significantly higher with TMS than in the control situation (Fig. 2 *A* and *B*; ANOVA analysis of arcsin-transformed fractions; $P = 0.037$, $F = 5.19$, df = 1,17).

Corrections that were performed in two stages, i.e., from start button (SB) to middle button (MB) and then to left button (LB)/right button (RB) (see Fig. 3), were included in the analysis,

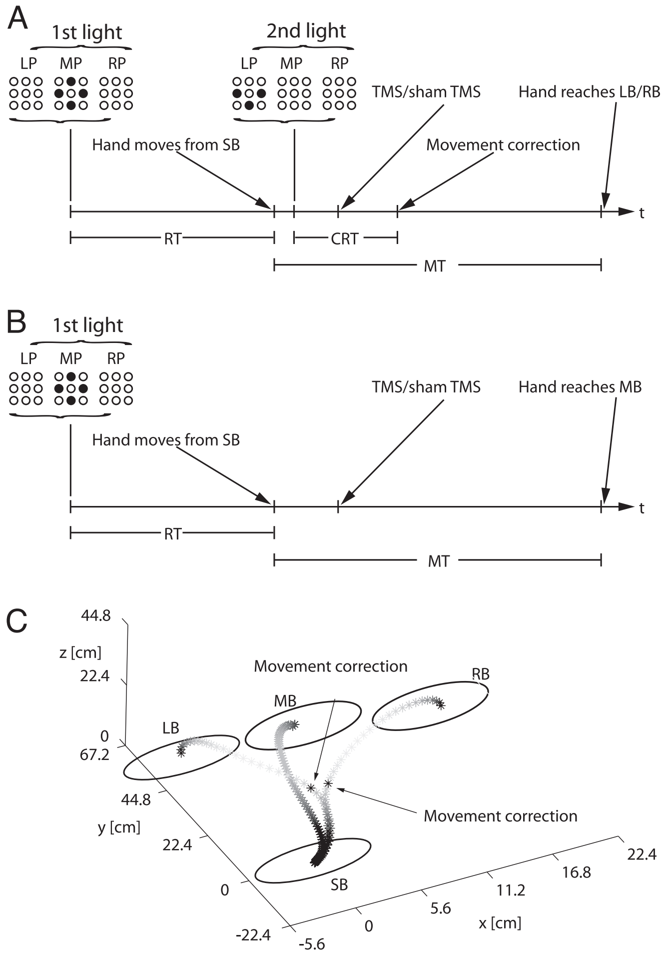

Fig. 3. Diagram of experiment. (*A*) Timeline of a trial with a correction. First, light is displayed in the MP as a diamond shape. After the visuomotor RT, the hand is lifted from the SB toward the MB. After ≈7 ms, a second light is displayed in (either) the LP (or RP). Then, after a fixed time interval (90 ms), either the TMS or sham TMS is applied. After the CRT, the movement is corrected away from the original direction toward the LB (or RB). The total time from when the hand is moved from the SB until it reaches the LB (or RB or MB) is the total MT. (*B*) Time line of a trial without correction. (*C*) Example from a single subject in which a normal trajectory is displayed (color coding corresponds to *z*-value, where the brightest point is the maximum *z*-value corresponding to 50% gray), which is calculated as the mean of all trials toward the MB and two trials (color coding corresponds to *z*-value, where brightest point is the maximum *z*-value corresponding to 10% gray) with corrections toward either the LB or RB. The time point of movement correction is indicated (in black).

but CRT was calculated as the time from SB to MB. Two subjects performed all (S8) or nearly all (S9) of their corrections in that way.

Perception–Action Interaction. We used a logistic regression model to test if the MT influenced whether subjects were able to perform a corrective movement. The ability to perform a correct correction (measured as the fraction of correct corrections) was the dependent variable. The clarity, MT, and the interaction between clarity and MT were independent variables. The model was significant $P = 0.0013$, but none of the independent variables was able to explain the ability to correct movements (clarity, $P = 0.94$; MT, $P = 0.87$; interaction, $P = 0.68$). We further tested whether there was interaction between CRT and clarity and RT and clarity. There was no significant interaction between CRT and clarity and RT and clarity. These results are described in more detail in *SI Results*.

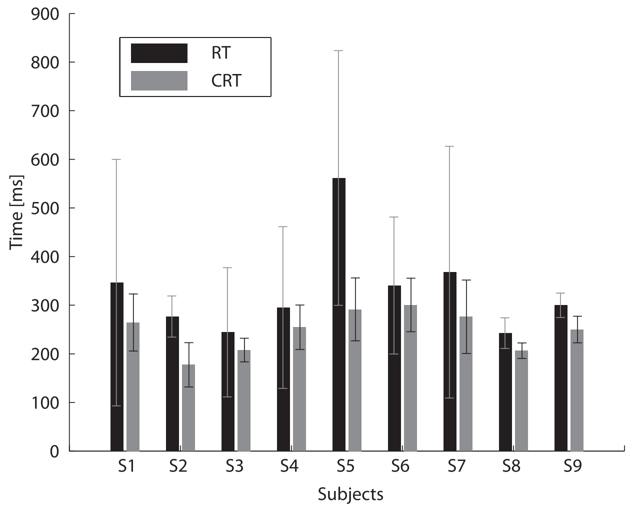

Fig. 4. The RT and CRT for each subject is shown. Error bars indicate ±1 standard deviation.

Efference Copy in Movement Correction. We tested whether there was a difference in RT and CRT. CRT was significantly lower than RT as revealed by a one-tailed paired Student's *t* test ($P = 0.005$, $t = 3.34$, df $= 8$). The mean RTs and CRTs are shown on Fig. 4 for each subject.

Discussion

TMS applied to the visual cortex decreased the ability to correctly identify the appearance of a second light that appeared during the reaching movement for a target. The confidence of detection was also reduced. This observation supports previous findings of the effects of TMS on target detection when applied to the primary visual cortex (11) and the effects on perceptual clarity when applied over the temporal lobe in a purely visual task (12, 13).

Critically, the loss of perception of the second light after TMS did not prevent the subjects from making appropriate corrective movements to reach for the second light. Corrections occurred even at the lowest level of perceptual confidence. This finding indicates that it is possible to induce blindsight-like behavior in healthy subjects, reaching toward "unseen" objects. This effect is present despite the structural integrity of the brain. So, as in previous reports (15, 16), the blindsight phenomenon is not confounded by injury or postinjury neuroplasticity. One can therefore better characterize the neural mechanisms of visual perception and visually guided action, and the differences between them, which may thereby explain the phenomenon of blindsight after TMS.

It has been suggested that an important mechanism for the ability to perform fast corrections of goal-directed movement is an efference copy (9). Evidence in favor of the involvement of an efference copy in movement correction in our study comes from the difference in CRT and RT. This difference has been suggested to indicate that an efference copy is involved in online movement correction (9). The argument is that the initial motor reaction time, when the subject reaches toward the first target (MB), requires that the visual signal is processed via the visual cortex to motor regions of the brain. The advantage of an efference copy is that already at a very early point in the movement process any deviation in the performed movement from the intended movement can be adjusted. Hence, lower reaction time during the correction can be accomplished compared with the initial motor reaction time.

Furthermore, our results suggest that the mechanism responsible for fast visually guided corrective movements lies outside visual cortex and that the visual signals used for correction of movements bypass visual cortex. There may be subcortical routes for visually guided reaching that bypass the cortical regions affected by TMS. Day and Brown (22) demonstrated subcortical involvement in visual control of reaching in an acallosal patient. There was a delay compared with normal volunteers in a simple crossed visuomotor reaction task. However, during a fast reaching task, similar to ours, no difference was found between the acallosal patient and the normal controls. This finding indirectly suggests that subcortical processes are sufficient to provide the information needed for fast correction of reaching movements.

Cats are able to perform fast corrective movements in a paradigm very similar to ours (3). The responsible neural circuitry involved in feline online movement correction involves propriospinal neurons in the cervical spine. The subcircuitry for fast corrective movements, as quick as 50–70 ms after target shift, was suggested to be the retino-tectospinal and retino-tecto-recticulospinal pathways. This network in the brainstem completely bypasses visual cortex. If such networks exist in humans, they may be responsible for fast corrective movements without accompanying perception. Interestingly, the networks in the cats responsible for these reaching movements do involve an efference copy, which is signaled from the propriospinal neurons to the cerebellum via the lateral reticular nucleus (4). Another possibility is that humans require cortical processing of the visual stimulus to perform the corrective movement.

In humans, an alternative subcortical route has been proposed. The information sufficient to perform corrective movements, without being aware of the presence of a visual stimulus, may be processed from superior colliculus through pulvinar to the parietal cortex (7, 8). The strong connectivity between parietal and motor/premotor regions may then provide programming of the motor program required to perform the corrective movement [shown by the effect of TMS over the posterior parietal cortex (23)]. The presence of this route from superior colliculus to parietal cortex in humans is further supported by anatomical diffusion tensor imaging studies (24).

Although we did observe that CRT was significantly lower than RT, we did not see corrections as quick as previously reported from human studies (121–154 ms) (22). This observation may be related to the way CRT was defined, or that movements were performed very fast in our study. In the study by Castiello *et al.* (10), MT was in the order of 500–600 ms for a movement which was 33% shorter in distance to ours but to a smaller target requiring greater precision. Another possibility is that corrections performed during movements are mechanically easier to perform than movements initiated from a stationary position.

We hypothesized that there would be an interaction between perception and action. However, none of the supplementary tests revealed any such effect on CRT, RT, or MT (see *SI Results*), nor did we observe that subjects were better at performing the corrections when they moved at different speeds. We could not find evidence supporting an interaction between perception and action. However, the supplementary results indicate that the same neural mechanisms underlie reaching corrections with and without perception of target switches.

Conclusion

We have shown that blindsight-like behavior can be induced in healthy subjects such that they can perform fast corrective reaching movements without being aware of the presence of the visual signal that guides behavior. Our results support previous proposals suggesting that an efference copy is involved in the movement correction. Interestingly, the mechanism seems to be the same regardless of how clearly target switches are perceived.

Materials and Methods

Subjects. Eleven healthy adult subjects took part in the experiment (mean age 28.1 years, range 20–44 years). All subjects gave their informed written consent. The study was performed according to the Declaration of Helsinki (1964) and approved by the local ethics committee. Of the eleven subjects who took part in the experiment, two were discarded. One subject reported seeing light after TMS, indicating that phosphenes were induced by the TMS. The induction of phosphenes occurred in 19 trials, and the subject consequently performed corrective movement after TMS in 38 trials without a second light. For the other subject, there was no effect of TMS with respect to the ability to report the shape of the arrow figure as shown in Fig. 1.

Setup. A start button (SB) was placed in front of the subject slightly to the right, making it possible for subjects to place the right hand on SB. One target button was placed in the middle [middle button (MB)], 52 cm ahead of the SB. Alternative target buttons were placed on either side of MB, one 9.5 cm to the right [right button (RB)] and another 9.5 cm to the left (LB). All buttons had a diameter of 9 cm. A 3×3 light-emitting diode (LED) grid panel was placed above each of the three target buttons [middle panel (MP), right panel (RP), and left panel (LP)]. The light presented in MP consisted of four LEDs in the grid that was lit, forming a 45°-tilted square, i.e., a diamond shape. The light was controlled by a 1401 Micro CED (Cambridge Electronic Design) and a laptop personal computer running Signal 2.5 (Cambridge Electronic Design). The lights in RP and LP were controlled by 1401 CED and a desktop personal computer running Signal 2.5. Trigger pulses from SB were used to trigger the TMS and the second lights. Movement trajectories were recorded at 120 Hz with three Qualisys infrared cameras controlled by a laptop personal computer. A circular shaped reflective sticker was applied to the middle finger. All trigger pulses, light presentations, and TMS stimuli were synchronized with the cameras by using a Qualisys analog sampling board sampling at 2,400 Hz.

TMS Stimulation. TMS was applied by using a Magstim 200 (Magstim) and a circular coil with an outer diameter of 13.5 cm and an inner diameter of 5 cm. The coil was placed just above the inion tangentially to the scalp. Stimulation intensity was 100% of stimulator output. However, if subjects reported that the stimulation at 100% was uncomfortable, the intensity was lowered to a more comfortable level, typically 80% or 90% of stimulator output.

Task and Visual Presentation. Each subject performed 200 trials. Before all trials, subjects placed their right hand on the SB. All trials were initiated by a diamond shaped light presented in the MP. The subject then reached toward the MB. In ≈80 trials, a second light was presented in either the RP or LP (≈40 in each) 7 ms after the hand was released from the SB. All trials were randomized but with a weighting factor that ensured that the RP and LP were presented in ≈40 trials each. The subject's task was to try and reach for the matching button (RB or LB) during the movement. The second light took one of four shapes, arrow pointing up, pointing left, pointing down, or pointing right. Each of the arrows consisted of three LEDs that were lit for 20–800 microseconds. Amassian *et al.* (25) used a recognition rate of ≈50% before TMS was applied, and because no mask was used in this experiment, the duration of the LEDs was adjusted through the experiment to account for unwanted effects of attentional drift.

After an additional 80 or 90 ms, TMS stimulation was applied over visual cortex or similar sham TMS stimulation. In the trials without a second light, TMS/sham TMS was applied 87 or 97 ms after the hand was released from the SB. The order of TMS/sham TMS was randomized with a weighting factor of 50% of each kind across the 200 trials. Subjects reached toward the target button, and when the target button was hit, a trigger signal was recorded.

After each trial, subjects reported verbally whether they had performed a corrective movement to the RB or LB or none. Then, they reported which arrow-like figure they had perceived, if any, in either the RP or LP, and, finally, they reported on a scale from 1 to 5 (C1–C5) how clearly they had perceived the arrow-like figure. Subjects' immediate responses were used. C1 corresponds to "no perception of a stimulus." C2 corresponds to a "possible vague perception of a stimulus without the ability to identify it." C3 corresponds to a "definite perception of a stimulus without the ability to identify it." C4 corresponds to a "definite perception of a stimulus with the possible ability to identify it." C5 corresponds to a "definite perception of a stimulus with a definite ability to identify it."

Data Analysis. All subjective reports were written in electronic format. The trajectory recorded from the Qualisys was converted into a 3D curve and exported to a text file for further analysis in Matlab 7.1. The analog data containing information about trigger pulses, visual display, and TMS pulses were also converted into text files for further analysis in Matlab.

Kinematical Analysis. For all trials, MT and RT were calculated. The CRT was calculated as described below.

CRT Deviation from Normal Curve. A normal curve from the SB to MB was calculated for each subject as the mean position across all trials without a second light. In trials with a second light, the first deviation corresponding to a kink on the movement trajectory was used as the time point corresponding to a correction away from the normal curve. To guide this manual measure, lines corresponding to ± 1 standard deviation of the normal curve were superimposed on the 3D graphs. The visual inspection of the trajectories with correction was performed by superimposition of the trajectory onto the mean trajectory of all trials without correction and blinded to which condition was present. The time point with deviation was identified and used to calculate CRT. CRT was calculated as the time from when the second light was displayed in either the LP or RP and the first visible sign of a deviation away from the mean trajectory. In the cases where subjects performed two-step corrections, the CRT was calculated as the time it took to move from the SB to MB, and the MT was calculated as the time from the SB to either the LB or RB.

1. Sanders MD, Warrington EK, Marshall J, Weiskrantz L (1974) *Lancet* 303:707–708.
2. Weiskrantz L, Warrington EK, Sanders MD, Marshall J (1974) *Brain* 97:709–728.
3. Alstermark B, Gorska T, Lundberg A, Pettersson L-G (1990) *Exp Brain Res* 80:1–11.
4. Alstermark B, Isa T, Pettersson LG, Sasaki S (2007) *Acta Physiol* 189:123–140.
5. Alstermark B, Isa T, Ohki Y, Saito Y (1999) *J Neurophysiol* 82:3580–3585.
6. Pierrot-Deseilligny C, Milea D, Muri RM (2004) *Curr Opin Neurol* 17:17–25.
7. Milner AD, Goodale MA (1995) in *The Visual Brain in Action* (Oxford Univ Press, Oxford).
8. Weiskrantz L (2002) in *Blindsight: A Case Study and Implications* (Oxford Univ Press, Oxford).
9. Angel RW (1976) *Neurology* 26:1164–1168.
10. Castiello U, Pulignan Y, Jeannerod M (1991) *Brain* 114:2639–2655.
11. Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB, Rudell AP, Eberle L (1989) *Electroencephalogr Clin Neurophysiol* 74:458–462.
12. Ramsøy TZ, Overgaard M (2004) *Phenomenol Cog Sci* 3:1–23.
13. Overgaard M, Rote J, Mouridsen K, Ramsøy TZ (2006) *Conscious Cog* 15:700–708.
14. Zeki S, Ffytche D (1998) *Brain* 121:25–45.
15. Kolb FC, Braun J (1995) *Nature* 377:336–338.
16. Boyer JL, Harrison S, Ro T (2005) *Proc Natl Acad Sci USA* 102:16875–16879.
17. Cotterill RMJ (2001) *Prog Neurobiol* 64:1–33.
18. Hommel B, Müsseler J, Aschersleben G, Prinz W (2001) *Behav Brain Sci* 24:849–937.
19. Rees G, Kreiman G, Koch C (2002) *Nat Rev Neurosci* 3:261–270.
20. Christensen MS, Ramsøy TZ, Madsen KH, Lund TE, Rowe JB (2006) *NeuroImage* 31:1711–1725.
21. Gottlieb J (2007) *Neuron* 53:9–16.
22. Day BL, Brown P (2001) *Brain* 124:1832–1840.
23. Desmurget M, Epstein CM, Turner RS, Prablanc C, Alexander GE, Grafton ST (1999) *Nat Neurosci* 2:563–567.
24. Rushworth MFS, Behrens TEJ, Johansen-Berg H (2006) *Cereb Cortex* 16:1418–1430.
25. Amassian VE, Cracco RQ, Maccabee PJ, Cracco JB, Rudell AP, Eberle L (1998) *J Clin Neurophysiol* 15:288–304.